

VINORELBINE- vinorelbine injection
Ingenus Pharmaceuticals, LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VINORELBINE INJECTION safely and effectively. See full prescribing information for VINORELBINE INJECTION

VINORELBINE injection, for intravenous use
Initial U.S. Approval:1994

WARNING: MYELOSUPPRESSION

See full prescribing information for complete boxed warning.

- Severe myelosuppression resulting in serious infection, septic shock, and death can occur (5.1) .
- Decrease the dose or withhold vinorelbine injection in accord with recommended dose modifications (2.2).

----- **INDICATIONS AND USAGE** -----

Vinorelbine injection is a vinca alkaloid indicated:

- In combination with cisplatin for first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) (1)
- As a single agent for first-line treatment of patients with metastatic NSCLC (1)

----- **DOSAGE AND ADMINISTRATION** -----

- In combination with cisplatin: 25 to 30 mg/m² as an intravenous injection or infusion once weekly (2.1)
- Single agent: 30 mg/m² as intravenously once a week (2.1)
- Adjust dose in patients with decreased neutrophil counts or elevated serum total bilirubin (2.2)

----- **DOSAGE FORMS AND STRENGTHS** -----

- Injection: 10 mg/1 mL and 50 mg/5 mL in single dose vial (3)

----- **CONTRAINDICATIONS** -----

None (4)

----- **WARNINGS AND PRECAUTIONS** -----

- Hepatic Toxicity: Monitor hepatic function prior to initiation and during treatment (5.2)
- Severe constipation and bowel obstruction, including necrosis and perforation, occur. Institute a prophylactic bowel regimen to mitigate potential constipation, bowel obstruction and/or paralytic ileus (5.3)
- Extravasation can result in severe tissue injury, local tissue necrosis and/or thrombophlebitis. Immediately stop vinorelbine injection and institute recommended management procedures (5.4)
- Neurologic Toxicity: Severe sensory and motor neuropathies occur. Monitor patients for new or worsening signs and symptoms of neuropathy. Discontinue for Grade 2 or greater neuropathy (5.5)
- Pulmonary toxicity and respiratory failure occur. Interrupt vinorelbine injection in patients who develop unexplained dyspnea or have any evidence of pulmonary toxicity. Permanently discontinue for confirmed interstitial pneumonitis or ARDA (5.6)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to the fetus and to use effective contraception (5.7, 8.1, 8.3)

----- **ADVERSE REACTIONS** -----

Most common adverse reactions (incidence ≥ 20%) are leukopenia, neutropenia, anemia, increased aspartate aminotransferase, nausea, vomiting, constipation, asthenia, injection site reaction and peripheral neuropathy (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ingenus Pharmaceuticals, LLC at 1-877-748-1970 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- **DRUG INTERACTIONS** -----

- Inhibitors of CYP3A4: May cause earlier onset and/or increased severity of adverse reactions (7.1)

----- **USE IN SPECIFIC POPULATIONS** -----

Lactation: Advise not to breastfeed (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2020

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FULL PRESCRIBING INFORMATION

WARNING: MYELOSUPPRESSION

- Severe myelosuppression resulting in serious infection, septic shock, hospitalization and death can occur (5.1) .
- Decrease the dose or withhold vinorelbine injection in accord with recommended dose modifications (2.2).

1 INDICATIONS AND USAGE

Vinorelbine injection is indicated:

- In combination with cisplatin for first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC)
- As a single agent for the treatment of patients with metastatic NSCLC

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

In Combination with Cisplatin 100 mg/m²

- The recommended dosage of vinorelbine injection is 25 mg/m² administered as an intravenous injection or infusion over 6 to 10 minutes on Days 1, 8, 15 and 22 of a 28-day cycle in combination with cisplatin 100 mg/m² on Day 1 only of each 28-day cycle.

In Combination with Cisplatin 120 mg/m²

- The recommended dosage of vinorelbine injection is 30 mg/m² administered as an intravenous injection or infusion over 6 to 10 minutes once a week in combination with cisplatin 120 mg/m² on Days 1 and 29, then every 6 weeks.

Single Agent

- The recommended dosage of vinorelbine injection is 30 mg/m² administered intravenously over 6 to 10 minutes once a week.

2.2 Dosage Modifications

Myelosuppression

Hold or decrease the dose of vinorelbine injection in patients with decreased neutrophil counts according to the following schema [see *Warnings and Precautions* (5.1)]:

Neutrophils on Day of Treatment (cells/mm ³)	Percentage of Starting Dose of Vinorelbine Injection, USP
≥ 1,500	100%
1,000 to 1,499	50%
< 1,000	Do not administer vinorelbine injection. Repeat neutrophil count in one week. If three consecutive weekly doses are held because neutrophil count is <1,000 cells/mm ³ , discontinue vinorelbine injection
Note: For patients who experience fever and/or sepsis while neutrophil count is < 1,500 cells/mm ³ or had 2 consecutive weekly doses held due to neutropenia, subsequent doses of vinorelbine injection should be:	
> 1,500	75%
1,000 to 1,499	37.5%
< 1,000	Do not administer vinorelbine injection. Repeat neutrophil count in one week.

Hepatic Impairment/Toxicity

Reduce vinorelbine injection dose in patients with elevated serum total bilirubin concentration according to the following schema [see *Warnings and Precautions (5.2) and Use in Specific Populations(8.6)*]:

Serum Total Bilirubin Concentration (mg/dl)	Percentage of Starting Dose of Vinorelbine Injection, USP
≤2.0	100%
2.1 to 3.0	50%
> 3.0	25%

Concurrent Myelosuppression and Hepatic Impairment/Toxicity

In patients with both myelosuppression and hepatic impairment/toxicity, administer the lower of the doses based on the corresponding starting dose of vinorelbine injection determined from the above schemas.

Neurologic Toxicity

Discontinue vinorelbine injection for Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 or higher peripheral neuropathy or autonomic neuropathy causing constipation [see *Warnings and Precautions (5.5)*].

2.3 Preparation and Administration

Preparation

Dilute vinorelbine injection in an intravenous bag to a concentration between 0.5 mg/mL and 2 mg/mL. Use one of the following recommended solutions for dilution:

- 5% Dextrose Injection, USP
- 0.9% Sodium Chloride Injection, USP
- 0.45% Sodium Chloride Injection, USP
- 5% Dextrose and 0.45% Sodium Chloride Injection, USP
- Ringer's Injection, USP
- Lactated Ringer's Injection, USP

Stability and Storage Conditions of Diluted Solutions

Diluted vinorelbine injection may be used for up to 24 hours under normal room light when stored in polyvinyl chloride bags at 5° to 30°C (41° to 86°F).

Administration

Administer diluted vinorelbine injection over 6 to 10 minutes into the side port of a free-flowing intravenous line followed by flushing with at least 75 to 125 mL of one of the solutions.

Vinorelbine injection must only be administered intravenously. It is extremely important that the intravenous needle or catheter be properly positioned before any vinorelbine injection is injected.

Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. If particulate matter is seen, vinorelbine injection should not be administered.

Management of Suspected Extravasation

If vinorelbine injection leakage into surrounding tissue occurs or is suspected, immediately stop administration of vinorelbine injection and initiate appropriate management measures in accordance with institutional policies [See *Warnings and Precautions (5.4)*].

2.4 Procedure for Proper Handling and Disposal

Vinorelbine injection is a cytotoxic drug. Follow applicable special handling and disposal procedures¹. Exercise caution in handling and preparing the solution of vinorelbine injection. The use of gloves is recommended. If the solution of vinorelbine injection contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

Avoid contamination of the eye with vinorelbine injection. If exposure occurs, flush the eyes with water immediately and thoroughly.

Discard unused portion.

3 DOSAGE FORMS AND STRENGTHS

Injection: 1 mL (10 mg/ 1 mL) and 5 mL (50 mg/ 5 mL) clear colorless to pale yellow solution in single-dose vial.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Myelosuppression, manifested by neutropenia, anemia and thrombocytopenia, occur in patients receiving vinorelbine injection as a single agent and in combination with cisplatin [*Adverse Reactions* (6.1 , 6.2)]. Neutropenia is the major dose-limiting toxicity with vinorelbine injection. Grade 3-4 neutropenia occurred in 53% of patients treated with vinorelbine injection at 30 mg/m² per week. Dose adjustment due to myelosuppression occurred in 51% of patients (Study 2). In clinical trials with vinorelbine injection administered at 30 mg/m² per week, neutropenia resulted in hospitalizations for pyrexia and/or sepsis in 8% of patients. Death due to sepsis occurred in 1% of patients. Neutropenia nadirs occur between 7 and 10 days after dosing with neutropenia count recovery usually occurring within the following 7 to 14 days. Monitor complete blood counts prior to each dose of vinorelbine injection. Do not administer vinorelbine injection to patients with neutrophil counts <1,000 cells/mm³. Adjustments in the dosage of vinorelbine injection should be based on neutrophil counts obtained on the day of treatment [*Dosage and Administration* (2.2)].

5.2 Hepatic Toxicity

Drug-induced liver injury manifest by elevated aspartate aminotransferase (AST) and bilirubin occur in patients receiving vinorelbine injection as a single agent and in combination with cytotoxic agents. Assess hepatic function prior to initiation of vinorelbine injection and periodically during treatment. Reduce the dose of vinorelbine injection for patients who develop elevations in total bilirubin \geq 2 times upper limit of normal [*see Dosage and Administration* (2.2) and *Use in Specific Populations* (8.6)].

5.3 Severe Constipation and Bowel Obstruction

Severe and fatal paralytic ileus, constipation, intestinal obstruction, necrosis, and perforation occur in patients receiving vinorelbine injection. Institute a prophylactic bowel regimen to mitigate potential constipation, bowel obstruction and/or paralytic ileus, considering adequate dietary fiber intake, hydration and routine use of stool softeners.

5.4 Extravasation and Tissue Injury

Extravasation of vinorelbine injection can result in severe irritation, local tissue necrosis and/or thrombophlebitis. If signs or symptoms of extravasation occur, immediately stop administration of vinorelbine injection and institute recommended management procedures [*see Dosage and Administration* (2.2) and *Adverse Reaction* (6.1)].

5.5 Neurologic Toxicity

Sensory and motor neuropathies, including severe neuropathies, occur in patients receiving vinorelbine injection. Monitor patients for new or worsening signs and symptoms of neuropathy, such as paresthesia, hyperesthesia, hyporeflexia and muscle weakness while receiving vinorelbine injection. Discontinue vinorelbine injection for CTCAE Grade 2 or greater neuropathy [see *Dosage and Administration* (2.2) and *Adverse Reaction* (6.1)].

5.6 Pulmonary Toxicity and Respiratory Failure

Pulmonary toxicity, including severe acute bronchospasm, interstitial pneumonitis, acute respiratory distress syndrome (ARDS) occur in patients receiving vinorelbine injection. Interstitial pneumonitis and ARDS included fatalities. The mean time to onset of interstitial pneumonitis and ARDS after vinorelbine administration was one week (range 3 to 8 days) [see *Adverse Reactions* (6.1)]. Interrupt vinorelbine injection in patients who develop unexplained dyspnea or have any evidence of pulmonary toxicity. Permanently discontinue vinorelbine injection for confirmed interstitial pneumonitis or ARDS.

5.7 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, vinorelbine injection can cause fetal harm when administered to a pregnant woman. In animal reproduction studies in mice and rabbits, embryo and fetal toxicity were observed with administration of vinorelbine at doses approximately 0.33 and 0.18 times the human therapeutic dose, respectively.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with vinorelbine injection and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with vinorelbine injection and for 3 months after the final dose [see *Use in Specific Populations* (8.1, 8.3)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Myelosuppression [see *Warnings and Precautions* (5.1)]
- Hepatic Toxicity [see *Warnings and Precautions* (5.2)]
- Severe Constipation and Bowel Obstruction [see *Warnings and Precautions* (5.3)]
- Extravasation and Tissue Injury [see *Warnings and Precautions* (5.4)]
- Neurologic Toxicity [see *Warnings and Precautions* (5.5)]
- Pulmonary Toxicity and Respiratory Failure [see *Warnings and Precautions* (5.6)]

6.1 Clinical Trial Experience

Because clinical trials are conducted under varying designs and in different patient populations, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial and may not reflect the rates actually observed in clinical practice.

Single Agent

The data below reflect exposure to vinorelbine injection as a single agent administered at a dose of 30 mg/m² on a weekly basis to 365 patients enrolled in 3 controlled studies for metastatic NSCLC and advanced breast cancer. The population included 143 patients with previously untreated metastatic NSCLC (Study 3) who received a median of 8 doses of vinorelbine injection. The patients were aged 32 to 79 (median 61 years), 71% were male, 91% White, 48% had adenocarcinoma histology. The data also reflect exposure to vinorelbine injection in 222 patients with previously treated advanced breast cancer who received a median of 10 doses of vinorelbine injection. Vinorelbine injection is not indicated for the treatment of breast cancer.

Selected adverse reactions reported in these studies are provided in Tables 1 and 2. The most common adverse reactions (≥ 20%) of single agent vinorelbine injection were leukopenia, neutropenia, anemia, increased aspartate aminotransferase (AST), nausea, vomiting, constipation, asthenia, injection site reaction and peripheral neuropathy. The most common (≥ 5%) Grade 3 or 4 adverse reactions were

neutropenia, leukopenia, anemia, increased total bilirubin, increased AST, injection site reaction and asthenia.

Approximately 49% of patients with NSCLC who were treated with vinorelbine injection experienced at least one dose reduction due to an adverse reaction.

Thirteen percent of patients discontinued vinorelbine injection due to adverse reactions. The most frequent adverse reactions leading to vinorelbine injection discontinuation were asthenia, dyspnea, nausea, constipation, anorexia, myasthenia and fever.

Table 1: Hematologic Adverse Reactions Experienced in > 5% of Patients Receiving Vinorelbine Injection*†:

		All Patients (N=365) (%)	NSCLC (N= 143) (%)
Laboratory			
Hematologic			
Neutropenia	< 2,000 cells/mm3	90	80
	< 500 cells/mm3	36	29
Leukopenia	< 4,000 cells/mm3	92	81
	< 1,000 cells/mm3	15	12
Thrombocytopenia	< 100,000 cells/mm3	5	4
Anemia	< 11 g/dl	83	77
	< 8 g/dl	9	1
Hospitalizations due to neutropenic complications		9	8

*Grade based on modified criteria from the National Cancer Institute version 1.

†Patients with NSCLC had not received prior chemotherapy. The majority of the remaining patients had received prior chemotherapy.

Table 2: Non-hematologic Adverse Reactions Experienced in ≥ 5% of Patients Receiving Vinorelbine Injection*†:

	All Grades		Grades 3-4	
	All Patients (%)	NSCLC (%)	All Patients (%)	NSCLC (%)
Laboratory				
Hepatic				
AST increased (N=346)	67	54	6	3
Bilirubin increased (N=351)	13	9	7	5
Clinical				
Nausea	44	34	2	1
Asthenia	36	27	7	5
Constipation	35	29	3	2
Injection site reaction	28	38	2	5
Injection site pain	16	13	2	1
Neuropathy peripheral‡	25	20	<2	1
Vomiting	20	15	2	1
Diarrhea	17	13	1	1

Alopecia	12	12	≤1	1
Phlebitis	7	10	<1	1
Dyspnea	7	3	3	2

* Grade based on modified criteria from the National Cancer Institute version 1.

† Patients with NSCLC had not received prior chemotherapy. The majority of the remaining patients had received prior chemotherapy.

‡ Incidence of paresthesia plus hypesthesia.

Myelosuppression: In clinical trials, Grade 3-4 neutropenia, anemia and thrombocytopenia occurred in 69%, 9% and 1%, respectively of patients receiving single agent vinorelbine injection. Neutropenia is the major dose-limiting toxicity.

Neurotoxicity: Neurotoxicity was most commonly manifested as constipation, paresthesia, hyperesthesia and hyporeflexia. Grade 3 and 4 neuropathy was observed in 1% of the patients receiving single agent vinorelbine injection.

Injection Site Reactions: Injection site reactions, including erythema, pain at injection site and vein discoloration, occurred in approximately one third of patients; 5% were severe. Phlebitis (chemical phlebitis) along the vein proximal to the site of injection was reported in 10% of patients.

Cardiovascular Toxicity: Chest pain occurred in 5% of patients; myocardial infarction occurred in <0.1% of patients.

Pulmonary Toxicity and Respiratory Failure: Dyspnea (shortness of breath) was reported in 3% of patients; it was severe in 2%. Interstitial pulmonary changes were documented.

Other: Hemorrhagic cystitis and the syndrome of inappropriate ADH secretion were each reported in <1% of patients.

In Combination with Cisplatin

Table 3 presents the incidence of selected adverse reactions, occurring in ≥ 10% of vinorelbine injection treated patients reported in a randomized trial comparing the combination of vinorelbine injection 25 mg/m² administered every week of each 28-day cycle and cisplatin 100 mg/m² administered on day 1 of each 28-day cycle versus cisplatin alone at the same dose and schedule in patients with previously untreated NSCLC (Study 1).

Patients randomized to vinorelbine injection plus cisplatin received a median of 3 cycles of treatment and those randomized to cisplatin alone received a median of 2 cycles of treatment. The incidence of Grade 3 and 4 neutropenia was significantly higher in the vinorelbine injection plus cisplatin arm (82%) compared to the cisplatin alone arm (5%).

Thirty-five percent of the eligible patients in the combination arm required treatment discontinuation due to an adverse reaction compared to 19% in the cisplatin alone arm.

Four patients in the vinorelbine injection plus cisplatin arm died of neutropenic sepsis. Seven additional deaths were reported in the combination arm: 2 from cardiac ischemia, 1 cerebrovascular accident, 1 multisystem failure due to an overdose of vinorelbine injection and 3 from febrile neutropenia.

Table 3: Adverse Reactions Experienced by ≥ 10% of Patients on Vinorelbine Injection plus Cisplatin versus Single-Agent Cisplatin*.

	Vinorelbine Injection 25 mg/m ² plus Cisplatin 100 mg/m ² (N=212)		Cisplatin 100 mg/m ² (N=210)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)

Laboratory				
Hematologic				
Neutropenia	89	82	26	5
Anemia	89	24	72	<8
Leukopenia	88	58	31	<1
Thrombocytopenia	29	5	21	<2
Febrile neutropenia [†]	N/A	11	N/A	0
Renal				
Blood creatinine increased	37	4	28	<5
Clinical				
Malaise/Fatigue/Lethargy	67	12	49	8
Vomiting	60	13	60	14
Nausea	58	14	57	12
Decreased appetite	46	0	37	0
Constipation	35	3	16	1
Alopecia	34	0	14	0
Weight decreased	34	1	21	<1
Fever without infection	20	2	4	0
Hearing impaired	18	4	18	<4
Injection site reaction	17	<1	1	0
Diarrhea	17	<3	11	<2
Paraesthesia	17	<1	10	<1
Taste alterations	17	0	15	0
Peripheral numbness	11	2	7	<1
Myalgia/Arthralgia	12	<1	3	<1
Phlebitis/Thrombosis/Embolism	10	3	<1	<1
Weakness	12	<3	7	2
Infection	11	<6	<1	<1
Respiratory tract infection	10	<5	3	3

* Graded according to the standard SWOG criteria version 1.

† Categorical toxicity grade not specified

Table 4 presents the incidence of selected adverse reactions, occurring in $\geq 10\%$ of vinorelbine injection treated patients reported in a randomized trial of vinorelbine injection plus cisplatin, vindesine plus cisplatin and vinorelbine injection as a single agent in patients with stage III or IV NSCLC who had not received prior chemotherapy. A total of 604 patients received either vinorelbine injection 30 mg/m² every week plus cisplatin 120 mg/m² on Day 1 and Day 29, then every 6 weeks thereafter (N=207), vindesine 3 mg/m² for 6 weeks, then every other week thereafter plus cisplatin 120 mg/m² on Days 1 and Day 29, then every 6 weeks thereafter (N=193) or vinorelbine injection 30mg/m² every week (N=204).

Patients randomized to vinorelbine injection plus cisplatin received a median of 15 weeks of treatment, vindesine plus cisplatin 12 weeks and vinorelbine injection received 13 weeks. Grade 3 and 4 neutropenia was significantly greater in the vinorelbine injection plus cisplatin arm (78%) compared to vindesine plus cisplatin (48%) and vinorelbine injection as a single agent (53%). Neurotoxicity, including peripheral neuropathy and constipation, was reported in 44% (Grade 3-4, 7%) of the patients receiving vinorelbine injection plus cisplatin, 58% (Grade 3-4, 17%) of the patients receiving vindesine and cisplatin and 44% (Grade 3-4, 8.5%) of the patients receiving vinorelbine injection as a single agent.

Study discontinuation due to an adverse reaction was required in 27, 22 and 10% of the patients randomized to vinorelbine injection plus cisplatin, vindesine plus cisplatin and cisplatin alone arms, respectively.

Table 4: Adverse Reactions Experienced by ≥ 10 % of Patients from a Comparative Trial of Vinorelbine Injection Plus Cisplatin versus Vindesine Plus Cisplatin versus Single Agent Vinorelbine Injection*

	Vinorelbine Injection /Cisplatin [†]		Vindesine/Cisplatin [‡]		Vinorelbine Injection [§]	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Laboratory						
Hematologic						
Neutropenia	95	78	79	48	85	53
Leukopenia	94	57	82	27	83	32
Thrombocytopenia	15	4	10	3.5	3	0
Renal						
Blood creatinine increased	46	N/A	37	N/A	13	N/A
Clinical						
Nausea/Vomiting	74	30	72	25	31	2
Alopecia	51	7.5	56	14	30	2
Neurotoxicity [¶]	44	7	58	17	44	8.5
Diarrhea	25	1.5	24	1	12	0.5
Injection site reaction	17	2.5	7	0	22	2
Ototoxicity	10	2	14	1	1	0

*Grade based on criteria from the World Health Organization (WHO).

[†]N=194 to 207; all patients receiving Vinorelbine Injection/cisplatin with laboratory and non-laboratory data.

[‡]N=173 to 192; all patients receiving vindesine/cisplatin with laboratory and non-laboratory data.

[§]N=165 to 201; all patients receiving Vinorelbine Injection with laboratory and non-laboratory data.

^{||}Categorical toxicity grade not specified.

[¶]Neurotoxicity includes peripheral neuropathy and constipation

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of vinorelbine injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections: pneumonia

Immune system disorders: anaphylactic reaction, pruritus, urticaria, angioedema

Nervous system disorders: loss of deep tendon reflexes, muscular weakness, gait disturbance, headache

Ear and labyrinth disorders: vestibular disorder, hearing impaired

Cardiac disorders: tachycardia

Respiratory disorders: pulmonary edema

Vascular disorders: pulmonary embolism, deep vein thrombosis, hypertension, hypotension, flushing, vasodilatation

Gastrointestinal disorders: mucosal inflammation, dysphagia, pancreatitis

Skin disorders: generalized cutaneous reactions (rash), palmar-plantar erythrodysesthesia syndrome

Musculoskeletal and connective tissue disorders: jaw pain, myalgia, arthralgia

General disorders and administration site conditions: injection site rash, urticaria, blistering, sloughing of skin

Injury, poisoning and procedural complications: radiation recall phenomenon, dermatitis, esophagitis

Laboratory abnormalities: electrolyte imbalance including hyponatremia

Other: tumor pain, back pain, abdominal pain

7 DRUG INTERACTIONS

7.1 CYP3A Inhibitors

Exercise caution in patients concurrently taking drugs known to inhibit CYP3A. Concurrent administration of vinorelbine injection with a CYP3A inhibitor may cause an earlier onset and/or an increased severity of adverse reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action [see *Clinical Pharmacology (12.1)*], vinorelbine injection can cause fetal harm when administered to a pregnant woman. Available human data are insufficient to inform the drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies in mice and rabbits, embryo and fetal toxicity were observed with administration of vinorelbine at doses approximately 0.33 and 0.18 times the human therapeutic dose, respectively (see Data). Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In a mouse embryo-fetal development study, administration of a single dose of vinorelbine at a dose level of 9 mg/m² or greater (approximately 0.33 times the recommended human dose based on body surface area) was embryotoxic and fetotoxic. Vinorelbine was embryotoxic and fetotoxic to pregnant rabbits when administered every 6 days during the period of organogenesis at doses of 5.5 mg/m² (approximately 0.18 times the recommended human dose based on body surface area) or greater. At doses that did not cause maternal toxicity in either species, vinorelbine administration resulted in reduced fetal weight and delayed ossification.

8.2 Lactation

Risk Summary

There are no data on the presence of vinorelbine in human milk or its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in breastfed infants from vinorelbine, advise women not to breastfeed during treatment with vinorelbine injection and for 9 days after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating vinorelbine injection [see *Use in Specific Populations (8.1)*].

Contraception

Females

Vinorelbine injection can cause fetal harm when administered to pregnant women [*see Use in Specific Populations (8.1)*]. Advise female patients of reproductive potential to use effective contraception during treatment with vinorelbine injection and for 6 months after the final dose.

Males

Vinorelbine injection may damage spermatozoa [*see Nonclinical Toxicology (13.1)*]. Advise males with female sexual partners of reproductive potential to use effective contraception during treatment with vinorelbine injection and for 3 months after the final dose.

Infertility

Males

Based on animal findings, vinorelbine injection may impair fertility in males [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and effectiveness of vinorelbine injection in pediatric patients have not been established.

Results from a single-arm study of vinorelbine injection administered at the dose of 33.75 mg/m² (for 35 patients) or at the dose of 30 mg/m² (for 11 patients) every week for 6 weeks followed by 2 weeks of rest were evaluated (courses of 8 weeks). Forty-six patients age 1 to 25 (median 11 years) with recurrent solid malignant tumors, including rhabdomyosarcoma or undifferentiated sarcoma (N=21 patients), neuroblastoma (N= 4 patients) and central nervous system (CNS) tumors (N=21 patients), were enrolled. The most significant grade 3 or 4 hematological adverse reactions were neutropenia (70%) and anemia (33%). The most significant grade 3 or 4 non-hematological adverse reactions were motor (15%) or cranial (13%) neuropathy, hypoxia (13%) and dyspnea (11%). Objective tumor response was observed in 2 out of 21 patients with rhabdomyosarcoma or undifferentiated sarcoma. No objective tumor response was observed in patients with CNS tumors (N=21) or neuroblastoma (N=4).

8.5 Geriatric Use

Of the 769 number of patients who received vinorelbine injection as a single agent and in combination with cisplatin in studies 1, 2 and 3, 247 patients were 65 years of age or older. No overall differences in safety, efficacy and pharmacokinetic parameters were observed between these patients and younger patients [*see Clinical Pharmacology (12.3)*].

8.6 Hepatic Impairment

The influence of hepatic impairment on the pharmacokinetics of vinorelbine injection has not been evaluated, but the liver plays an important role in the metabolism of vinorelbine injection. Elevated AST occurs in >60% of the patients receiving vinorelbine injection as a single agent (6% Grade 3-4). Therefore, exercise caution in patients with hepatic impairment. Reduce the dose of vinorelbine injection for patients with elevated serum total bilirubin concentrations [*see Dosage and Administration (2.2) and Warnings and Precautions (5.2)*].

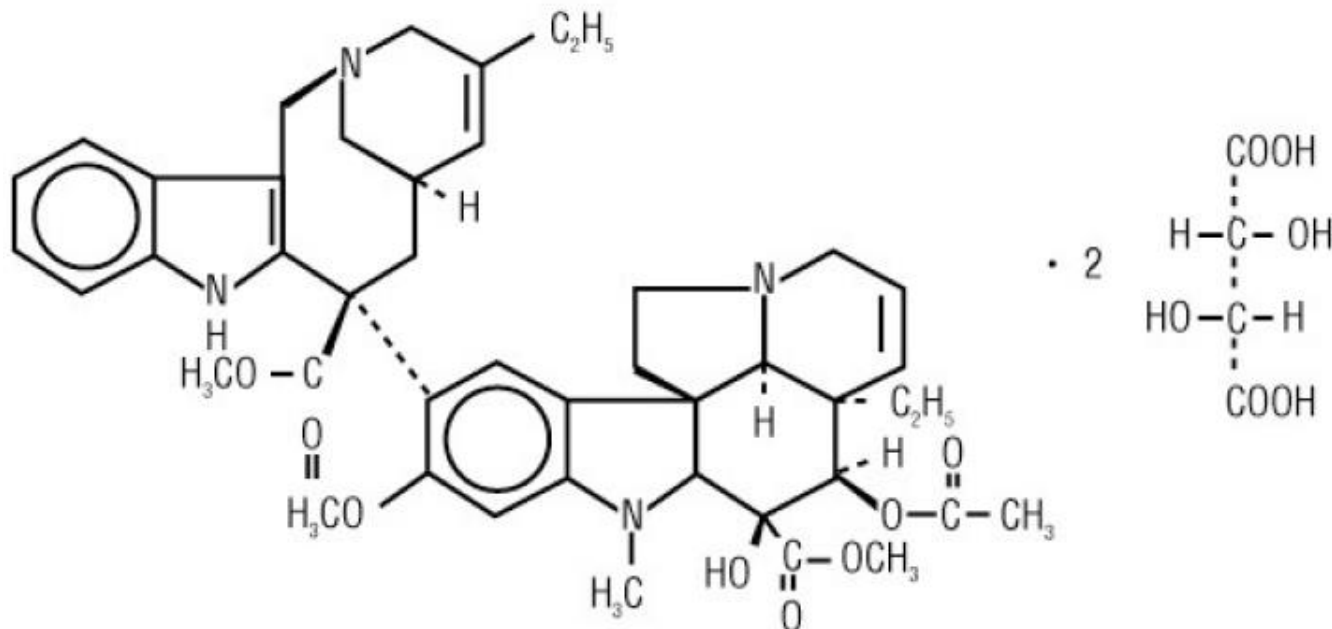
10 OVERDOSAGE

There is no known antidote for overdoses of vinorelbine injection. Overdoses involving quantities up to 10 times the recommended dose (30 mg/m²) have been reported. The adverse reactions described were consistent with those listed in the ADVERSE REACTIONS section, including paralytic ileus, stomatitis and esophagitis. Bone marrow aplasia, sepsis and paresis have also been reported. Fatalities have occurred following overdose of vinorelbine injection. If overdose occurs, general supportive measures together with appropriate blood transfusions, growth factors and antibiotics should be instituted as deemed necessary by the physician.

11 DESCRIPTION

Vinorelbine injection, USP contains vinorelbine tartrate, USP, a semi-synthetic vinca alkaloid. The

molecular formula for vinorelbine tartrate, USP is $C_{45}H_{54}N_4O_8 \cdot 2C_4H_6O_6$. It has a molecular weight of 1079.11. The structural formula is as follows.



Vinorelbine tartrate, USP is a white to almost white powder. It is freely soluble in water, in methanol and in 96% ethanol. It is practically insoluble in hexane.

Vinorelbine injection, USP is a sterile nonpyrogenic aqueous solution for intravenous use. Each millilitre of solution contains 10 mg vinorelbine (equivalent to 13.85 mg vinorelbine tartrate) in Water for Injection. The pH of Vinorelbine injection, USP is approximately 3.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vinorelbine is a vinca alkaloid that interferes with microtubule assembly. The antitumor activity of vinorelbine is thought to be due primarily to inhibition of mitosis at metaphase through its interaction with tubulin. Vinorelbine may also interfere with: 1) amino acid, cyclic AMP and glutathione metabolism, 2) calmodulin-dependent Ca^{++} -transport ATPase activity, 3) cellular respiration, and 4) nucleic acid and lipid biosynthesis. Vinorelbine inhibited mitotic microtubule formation in intact mouse embryo tectal plates at a concentration of 2 μ M inducing a blockade of cells at metaphase, but produced depolymerization of axonal microtubules at a concentration 40 μ M, suggesting a modest selectivity of vinorelbine for mitotic microtubules.

12.3 Pharmacokinetics

The pharmacokinetics of vinorelbine were studied in 49 patients who received doses of 30 mg/m² administered as 15- to 20-minute constant-rate infusions. Vinorelbine concentrations in plasma decay in a triphasic manner.

Distribution

Steady-state volume of distribution (V_{ss}) values range from 25.4 to 40.1 L/kg. Vinorelbine demonstrated high binding to human platelets and lymphocytes. The free fraction was approximately 0.11 in human plasma over a concentration range of 234 to 1169 ng/mL. The binding to plasma constituents in cancer patients ranged from 79.6% to 91.2%. Vinorelbine binding was not altered in the presence of cisplatin, fluorouracil, or doxorubicin.

Elimination

The terminal phase half-life averages 27.7 to 43.6 hours and the mean plasma clearance ranges from 0.97 to 1.26 L/hr/kg.

Metabolism

Vinorelbine undergoes substantial hepatic elimination in humans, with large amounts recovered in feces. Two metabolites of vinorelbine have been identified in human blood, plasma and urine; vinorelbine N-oxide and deacetylvinorelbine. Deacetylvinorelbine has been demonstrated to be the primary metabolite of vinorelbine in humans and has been shown to possess antitumor activity similar to vinorelbine. Therapeutic doses of vinorelbine (30 mg/m²) yield very small, if any, quantifiable levels of either metabolite in blood or urine. The metabolism of vinorelbine is mediated by hepatic CYP3A.

Excretion

After intravenous administration of radioactive vinorelbine, approximately 18% and 46% of administered radioactivity was recovered in urine and feces, respectively. In a different study, 10.9% ± 0.7% of a 30 mg/m² intravenous dose was excreted as parent drug in urine.

Specific Populations

Age has no effect on the pharmacokinetics (CL, V_{ss} and t_{1/2}) of vinorelbine.

Drug Interaction studies

The pharmacokinetics of vinorelbine are not influenced by the concurrent administration of cisplatin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of vinorelbine injection has not been studied. Vinorelbine has been shown to affect chromosome number and possibly structure in vivo (polyploidy in bone marrow cells from Chinese hamsters and a positive micronucleus test in mice). It was not mutagenic in the Ames test and gave inconclusive results in the mouse lymphoma TK Locus assay. Vinorelbine did not affect fertility to a statistically significant extent when administered to rats on either a once-weekly (9 mg/m², approximately one third the human dose) or alternate-day schedule (4.2 mg/m², approximately 0.14 times the human recommended dose) prior to and during mating. In male rats, administration of vinorelbine twice weekly for 13 or 26 weeks at dose levels of 2.1 and 7.2 mg/m² (approximately 0.07 and 0.24 times the recommended human dose), respectively, resulted in decreased spermatogenesis and prostate/seminal vesicle secretion.

14 CLINICAL STUDIES

14.1 Combination Use with Cisplatin

The safety and efficacy of vinorelbine injection in combination with cisplatin was evaluated in two randomized, multicenter trials.

Cisplatin 100mg/m²

Study 1 was a randomized, multicenter, open-label trial of vinorelbine injection plus cisplatin and cisplatin alone for the treatment of stage IV or stage IIIB NSCLC in patients with malignant pleural effusion or multiple lesions in more than one lobe of the ipsilateral lung who had not received prior chemotherapy. A total of 432 patients were randomized 1:1 to receive either vinorelbine injection 25 mg/m² on Day 1 then every week of each 28-day cycle plus cisplatin 100 mg/m² administered on Day 1 of each 28-day cycle (N=214) or single agent cisplatin 100 mg/m² on Day 1 of each 28-day cycle (N=218).

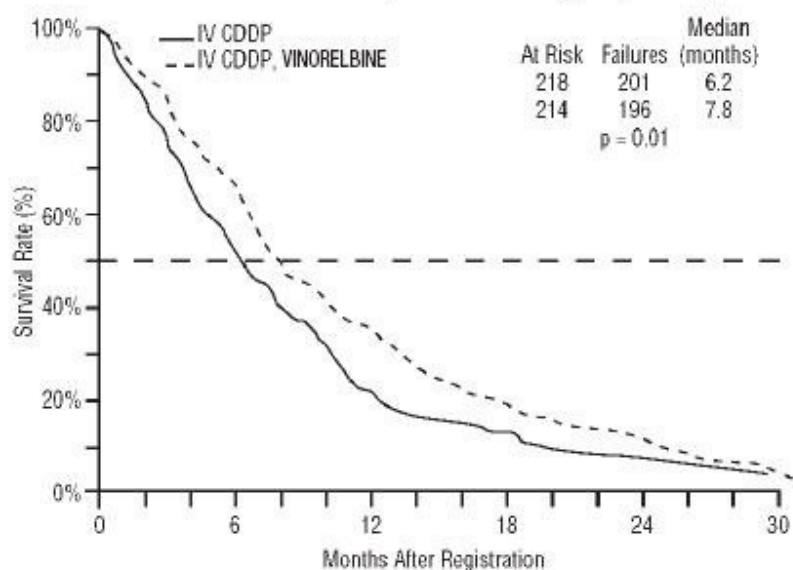
Patient demographics and disease characteristics were similar between arms. Of the overall study population, the median age was 64 (range 33-84), 66% were male, 80% were White, 92% had stage IV disease and 8% stage IIIB, 53% had adenocarcinoma, 21% squamous cell, 14% large cell histology. The major efficacy outcome measure was overall survival. The efficacy results are presented in Table

7 and Figure 1.

Table 7. Efficacy Results (Study 1)

	Vinorelbine Injection plus Cisplatin (N=214)	Cisplatin (N=218)
Overall Survival		
Median Survival in months (95% CI)	7.8 (6.9, 9.6)	6.2 (5.4, 7.7)
Unstratified log-rank p-value	0.01	
Overall Response rate (ORR)		
Evaluable patients	N = 206	N=209
ORR (95% CI)	19% (14%, 25%)	8% (5%, 13%)
Chi-square test p-value	<0.001	

Figure 1: Overall Survival VINORELBINE/Cisplatin versus Single-Agent Cisplatin



Cisplatin 120mg/m²

Study 2 was a randomized, 3-arm, open-label, multicenter trial of vinorelbine injection plus cisplatin, vindesine plus cisplatin and vinorelbine injection as a single agent for the treatment of patients with stage III or IV NSCLC who had not received prior chemotherapy. The study was conducted in Europe. A total of 612 patients were randomized 1:1:1 to receive vinorelbine injection 30 mg/m² every week of a 6-week cycle plus cisplatin 120 mg/m² on Day 1 and Day 29, then every 6 weeks thereafter (N=206); and vindesine 3 mg/m² for 6 weeks, then every other week thereafter plus cisplatin 120 mg/m² on Days 1 and Day 29, then every 6 weeks thereafter (N=200) or vinorelbine injection 30mg/m² every week of a 6-week cycle (N=206). The main efficacy outcome measure was to compare overall survival between vinorelbine injection plus cisplatin and vindesine plus cisplatin. The other efficacy outcome measure was to compare overall survival in the better of the two combination regimens to that vinorelbine injection as a single agent.

Patient demographics were in general similar between arms: the median age of the overall population was 60 years (range 30 to 75), 90% were male, 78% had WHO performance status of 0 or 1. Tumor characteristics were in general similar with the exception of histologic subtype of NSCLC. Adenocarcinoma was the histologic subtype in 32% of patients in the vinorelbine injection plus cisplatin arm, 40% of patients in vindesine plus cisplatin arm and 28% of patients on the vinorelbine injection arm. Ten percent of the patients had stage IIIA disease, 28% stage IIIB and 50% stage IV. Twelve percent of the patients had received prior surgery or radiotherapy.

The efficacy results of Study 2 are presented in Table 8.

Table 8. Efficacy Results (Study 2)

	Vinorelbine Injection (N=206)	Vinorelbine Injection plus cisplatin (N=206)	Vindesine plus Cisplatin (N=200)
Median survival in months (99.5% CI)	7.2 (5.4, 9.1)	9.2 (7.4, 11.1)	7.4 (6.1, 9.1)
Unstratified log-rank p-value	n/a ¹	0.087	
	0.05		n/a
Overall Response Evaluable Patients (ORR) (95% CI)	N=205 14% (10%, 20%)	N=203 28% (22%, 35%)	N=198 19% (14%, 25%)
Chi-square test p-value	n/a	0.03	
	< 0.001		n/a

¹n/a = not applicable

14.2 Single Agent

The safety and efficacy of vinorelbine injection as a single agent was evaluated in one randomized multicentre trial. Study 3 was a randomized, open-label clinical trial of vinorelbine injection or fluorouracil (FU) plus leucovorin (LV) in patients with Stage IV NSCLC who had not received prior chemotherapy. A total of 211 patients were randomized 2:1 to receive vinorelbine injection 30 mg/m² weekly of a 8-week cycle (N=143) or FU 425 mg/m² bolus intravenously plus LV 20 mg/m² bolus intravenously daily for 5 days of a 4-weeks cycle (N=68).

Patient demographics and disease characteristics were in general similar between arms. In the overall population, the median age was 61 years (range 32 - 83), 74% were male, 88% were White, 46% had adenocarcinoma histology. Fifty percent of the patients had Karnofsky performance status \geq 90 in the vinorelbine injection arm compared to 38% in the FU/LV arm.

The primary efficacy outcome of the study was overall survival. The median survival time was 30 weeks versus 22 weeks for patients receiving vinorelbine injection versus FU/LV, respectively (p=0.06). Partial objective responses were observed in 11.1% (95% CI=6.2%, 17.9%) and 3.5% (95% CI=0.4%, 11.9%) of patients who received vinorelbine injection and FU/LV, respectively.

15 REFERENCES

1. OSHA. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>

16 HOW SUPPLIED/STORAGE AND HANDLING

Vinorelbine injection, USP is a clear, colorless to pale yellow aqueous solution available in single-dose vial, individually packaged in a carton as:

- 10 mg/1 mL (NDC 50742-420-01).
- 50 mg/5 mL (NDC 50742-427-05).

Store the vials at 2° to 8°C (36° to 46°F). Protect from light. DO NOT FREEZE. Retain in carton until use. Unopened vials of Vinorelbine Injection, USP are stable at 25°C (77°F) for up to 72 hours. Store diluted solutions of Vinorelbine Injection, USP at 5° to 30°C (41° to 86°F) [see Dosage and Administration (2.3)].

Vinorelbine injection, USP is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹

17 PATIENT COUNSELING INFORMATION

Myelosuppression

Advise patients to contact a healthcare provider for new onset fever, or symptoms of infection

[see Warnings and Precautions (5.1)].

Constipation and Bowel Obstruction

Advise patients to follow a diet rich in fibers, drink fluids to stay well hydrated and use stool softeners to avoid constipation. Contact a health care provider for severe constipation, new onset abdominal pain, nausea and vomiting *[see Warnings and Precautions (5.3)].*

Neurologic Toxicity

Advise patients to contact a health care provider for new onset or worsening of numbness, tingling, decrease sensation or muscle weakness *[see Warnings and Precautions (5.5)].*

Pulmonary Toxicity

Advise patients to contact a healthcare provider for new onset or worsening of shortness of breath, cough, wheezing or other new pulmonary symptoms *[see Warnings and Precautions (5.6)].*

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.1, (8.3)]* .
- Advise females of reproductive potential to use effective contraception during treatment with vinorelbine injection and for 6 months after the final dose *[see Use in Specific Populations (8.3)]*.
- Advise males with female partners of reproductive potential to use effective contraception during treatment with vinorelbine injection and for 3 months after the final dose *[see Use in Specific Population (8.7) and Nonclinical Toxicology (13.1)]*.

Lactation

Advise women not to breastfeed during treatment with vinorelbine injection and for 9 days after the final dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males of reproductive potential that vinorelbine injection may impair fertility *[see Use in Specific Populations (8.3)]*.

Manufactured for:

Ingenus Pharmaceuticals, LLC

Orlando, FL 32839-6408

Made in Switzerland.

Revised: 02/2020

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL



NDC 50742-420-01

Vinorelbine Injection, USP

10 mg/mL

FOR INTRAVENOUS USE ONLY

MUST BE DILUTED

Sterile, nonpyrogenic

CYTOTOXIC AGENT

1 mL Single-Dose Vial

Rx only

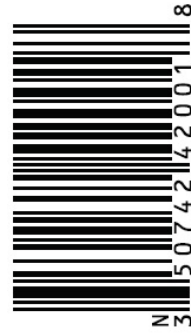
**Store the vials at 2° to 8°C
(36° to 46°F). Protect from light.
DO NOT FREEZE.**

Manufactured for:

Ingenus Pharmaceuticals, LLC
Orlando, FL 32839-6408

Made in Switzerland

420-01 v1/01-2019



LOT:

EXP:

Vinorelbine Injection Vial Label - 10mg/mL



NDC 50742-427-05

Vinorelbine Injection, USP

**50 mg/5 mL
(10 mg/mL)**

FOR INTRAVENOUS USE ONLY

MUST BE DILUTED

Sterile, nonpyrogenic

CYTOTOXIC AGENT

5 mL Single-Dose Vial

Rx only

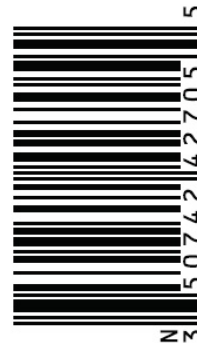
**Store the vials at 2° to 8°C
(36° to 46°F). Protect from light.
DO NOT FREEZE.**

Manufactured for:

Ingenus Pharmaceuticals, LLC
Orlando, FL 32839-6408

Made in Switzerland

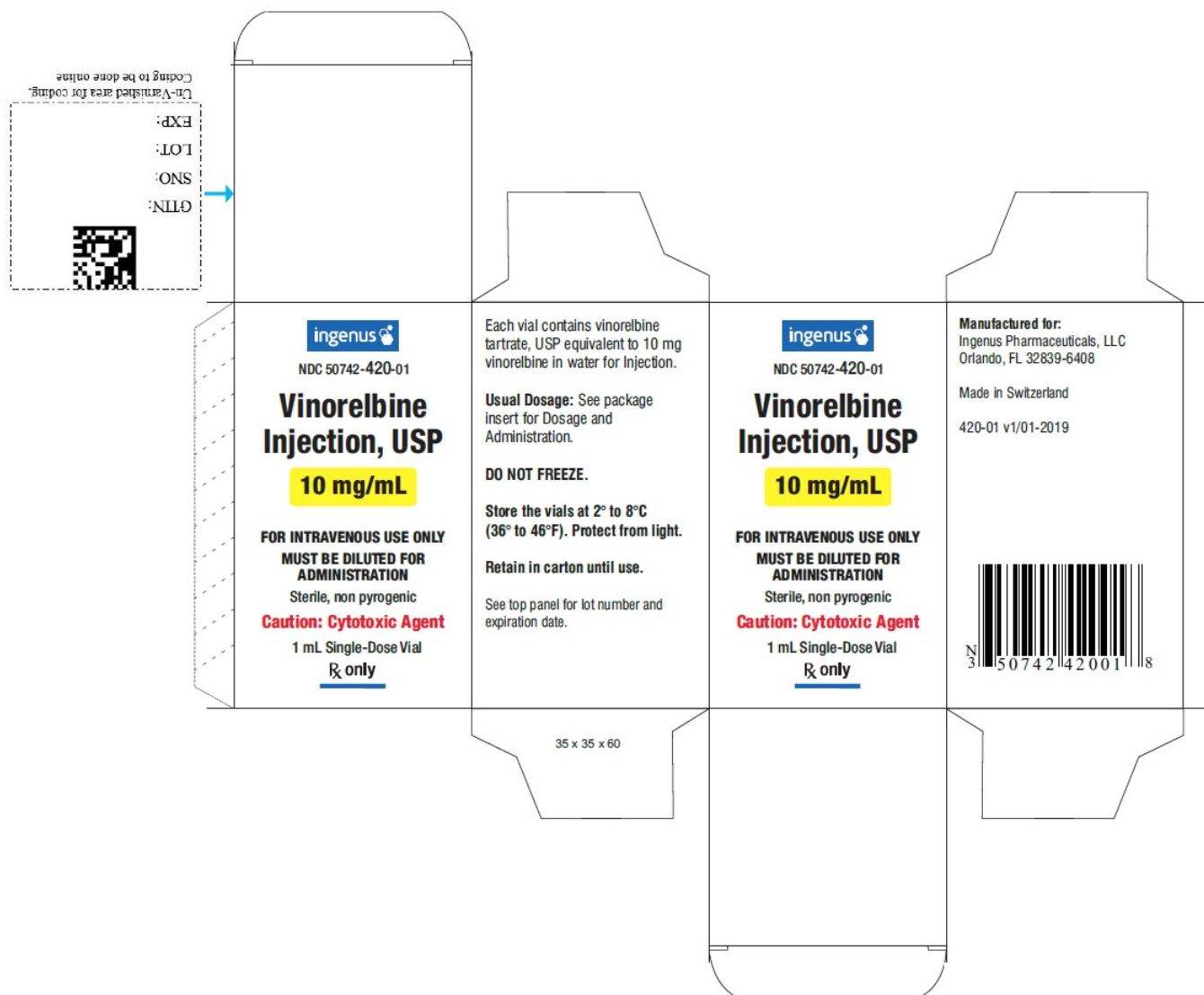
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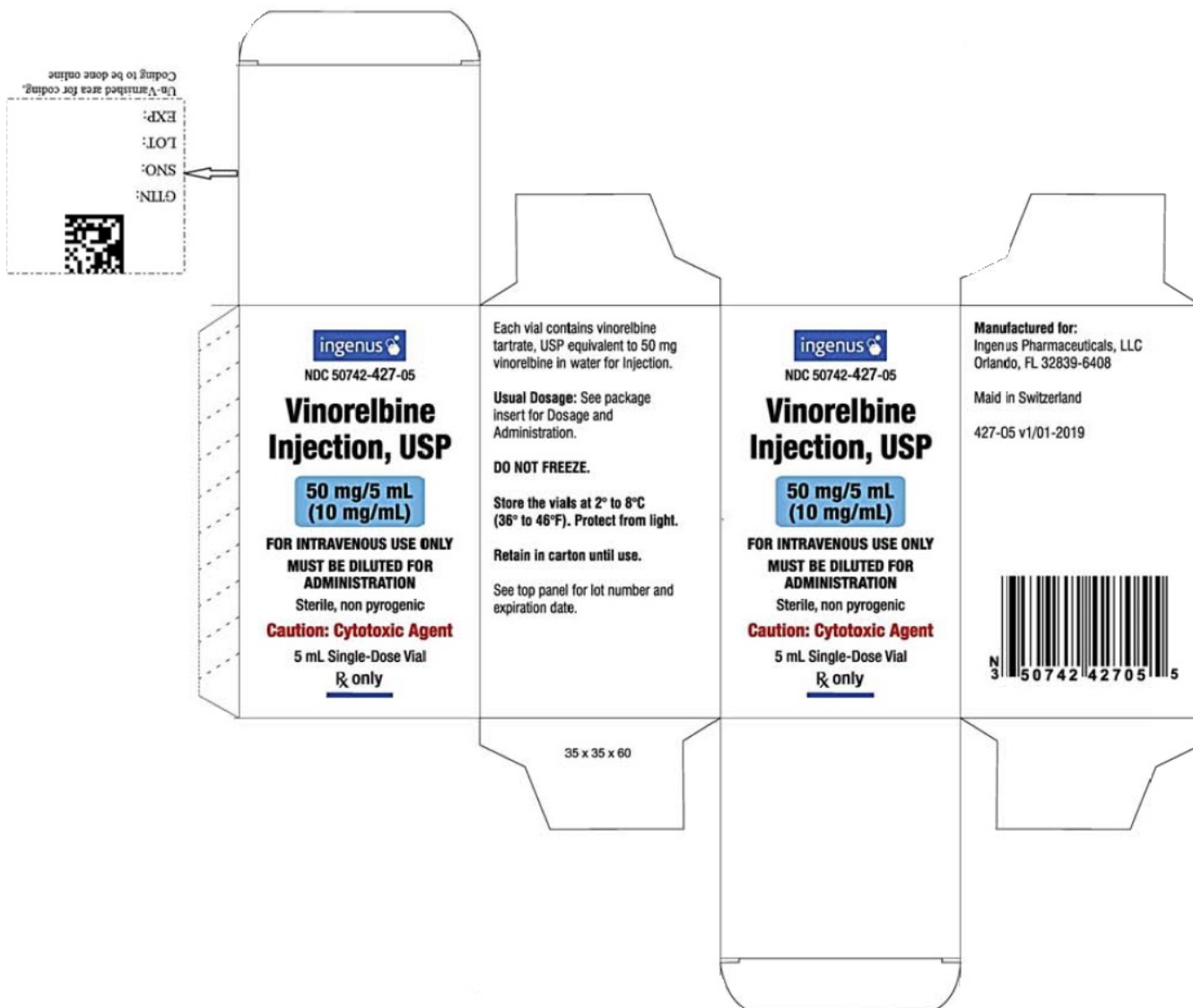
LOT:

EXP:

Vinorelbine Injection Vial Label - 50mg/5mL



Vinorelbine Injection Carton Label - 10mg/mL



Vinorelbine Injection Carton Label - 50mg/5mL



VINORELBINE

vinorelbine injection

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:50742-420
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
VINORELBINE TARTRATE (UNII: 253GQW851Q) (VINORELBINE - UNII:Q6C979R91Y)	VINORELBINE	10 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
-----------------	----------

WATER (UNII: 059QF0KO0R)				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50742-420-01	1 in 1 CARTON	08/08/2019	
1		1 mL in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA		ANDA208997	08/08/2019	

VINORELBINE				
vinorelbine injection				
Product Information				
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:50742-427	
Route of Administration	INTRAVENOUS			
Active Ingredient/Active Moiety				
Ingredient Name		Basis of Strength	Strength	
VINORELBINE TARTRATE (UNII: 253GQW851Q) (VINORELBINE - UNII:Q6C979R91Y)		VINORELBINE	50 mg in 5 mL	
Inactive Ingredients				
Ingredient Name		Strength		
WATER (UNII: 059QF0KO0R)				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50742-427-05	1 in 1 CARTON	08/08/2019	
1		5 mL in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
ANDA	ANDA208997	08/08/2019		

Labeler - Ingenus Pharmaceuticals, LLC (833250017)

Registrant - Novast Laboratories , Ltd. (527695995)

Establishment

Name	Address	ID/FEI	Business Operations
Ingenus Pharmaceuticals GmbH		482730327	ANALYSIS(50742-420, 50742-427) , LABEL(50742-420, 50742-427) , MANUFACTURE(50742-420, 50742-427) , PACK(50742-420, 50742-427) , STERILIZE(50742-420, 50742-427)

Revised: 2/2020

Ingenus Pharmaceuticals, LLC